(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002957 A1

(51) International Patent Classification[7]: C07D 211/78, 405/12, A61K 31/451, A61P 9/00

(21) International Application Number: PCT/EP2003/004445

(22) International Filing Date: 29 April 2003 (29.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP02/07102 27 June 2002 (27.06.2002) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL TETRAHYDROPYRIDINE DERIVATIVES AS RENIN INHIBITORS

(57) Abstract: The invention relates to novel tetrahydropyridine derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.

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NOVEL TETRAHYDROPYRIDINE DERIVATIVES AS RENIN INHIBITORS

The invention relates to novel compounds of the general formula **I**. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula **I** and especially their use as renin inhibitors in cardiovascular events and renal insufficiency. Furthermore, some of these compounds can be regarded as inhibitors of other aspartyl proteases and might therefore be useful as inhibitors of plasmepsins to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

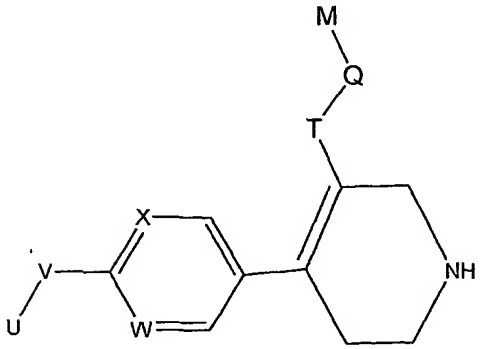
Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1996**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159; Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes to Ang II, whose concentration is dramatically increased by the blockade of AT_1 receptors. This may raise serious questions regarding the safety and efficacy profile of AT_1 receptor antagonists. In summary, renin inhibitors are not only expected to be different from ACE inhibitors and AT_1 blockers with regard to safety, but more importantly also with regard to their efficacy to block the RAS.

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, metabolically stable, orally bioavailable and sufficiently soluble renin inhibitors that can be prepared on a large scale are missing and sought. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il Farmaco*, **2001**, *56*, 21). However, the development status of these compounds is not known.

The present invention relates to the unexpected identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis, are described.

In particular, the present invention relates to novel compounds of the general formula I.



Formula I

wherein

X and W represent independently a nitrogen atom or a CH-group;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; $-COO-$; $-(CH_2)_pOCONR^1-$; $-(CH_2)_pN(R^{1'})CONR^1-$;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

R^1 and $R^{1'}$ independently represent hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5 or 6;
s is the integer 2, 3, 4 or 5;
t is the integer 1, 2, 3 or 4;
u is the integer 1, 2 or 3;
v the integer to 2, 3 or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

In the definitions of general formula I – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono-, di-, or trisubstituted independently by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1C(O)R^{1'}$, $-NR^1S(O)_2R^{1'}$, $-C(O)NR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono-, di-, tri-, tetra- or pentasubstituted independently by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1C(O)R^{1'}$, $-NR_1S(O)_2R^{1'}$, $-C(O)NR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy. Preferred substituents are halogen, lower alkoxy, lower alkyl.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of aryloxy groups is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which

rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

It is understoood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the general formula **I** and in claims 1 to 6 for clarity reasons but the definitions in formula **I** and in claims 1 to 6 should be read as if they are included therein.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula **I** is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula **I** can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts therof.
The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

A group of preferred compounds of general formula **I** are those wherein X, W, V, and U, are as defined in general formula **I** and wherein

T is $-CONR^1-$;
Q is a methylene;
M is hydrogen; aryl; heteroaryl.

Another group of more preferred compounds of general formula **I** are those wherein X, W, T, Q, and M are as defined in general formula **I** and wherein

V is one of the following groups:

$-CH_2CH_2O-$; $-CH_2CH_2CH_2O-$; $-OCH_2CH_2O-$

and U is as defined in general formula I above.

Another group of even more preferred compounds of general formula I are those wherein V, U, T, Q, and M are as defined in general formula I and wherein

X and W represent CH.

Another group of more preferred compounds of general formula I are those wherein X, W, V, Q, T, and M are as defined in general formula I and wherein

U is a mono-, di-, or trisubstituted phenyl. Preferred substituents are independently halogen or lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy.

Especially preferred compounds of general formula I are those selected from the group consisting of:

4-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid 2-phenethylmethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid (2-chlorobenzyl)methylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluorobenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*m*-tolyloxyethyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-fluorophenyl)ethyl]amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*o*-tolylethyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide,

4-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethylbenzyl)amide,

4-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide,

4-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropylphenethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropylphenethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*o*-tolylethyl)amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,4-dimethoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-6-fluorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-fluoro-2-methylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-difluorobenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-difluorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,4-dimethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)-cyclopropylamide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,3-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(4-chloro-2-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(5-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-difluorobenzyl)amide,

4-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,3-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxy-benzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(4-chloro-2-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-3,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-6-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,3-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide, and

4-{4-[2-(2,6-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide.

The compounds of general formula **I** and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. They may especially be used in the treatment and/or prophylaxis of cardiovascular and renal diseases. Examples of such diseases are hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure. They can also be used to prevent restenosis after balloon or stent angioplasty, to treat erectile dysfunction, glomerulonephritis, renal colic, and glaucoma. Furthermore, they can be used in the therapy and the prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, as well as other diseases presently known to be related to the RAS.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to the RAS such as hypertension,

coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure, which method comprises administering a compound as defined above to a human being or animal.

The invention further relates to the use of compounds of general formula **I** as defined above for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure. These medicaments may be prepared in a manner known per se.

The compounds of formula **I** may also be used in combination with one or more other therapeutically useful substances e. g. with other renin inhibitors, with ACE-inhibitors, with angiotensin-receptor antagonists, with diuretics, with calcium channel blockers, with endothelin receptors antagonists or with other drugs beneficial for the prevention or the treatment of cardiovascular events or renal insufficiency.

All forms of prodrugs leading to an active component comprised in general formula **I** are included in the present invention.

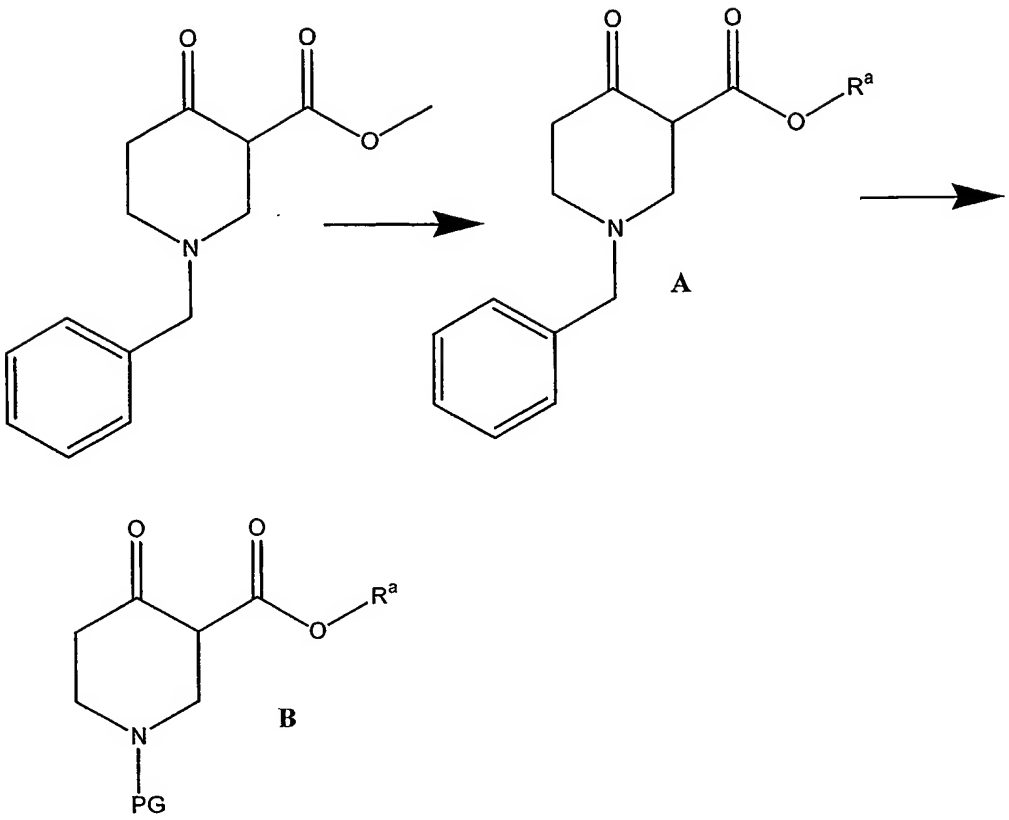
The compounds of general formula **I** can be manufactured by the methods given below, by the methods given in the examples or by analogous methods.

Preparation of the precursors:

Precursors are compounds that were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry.

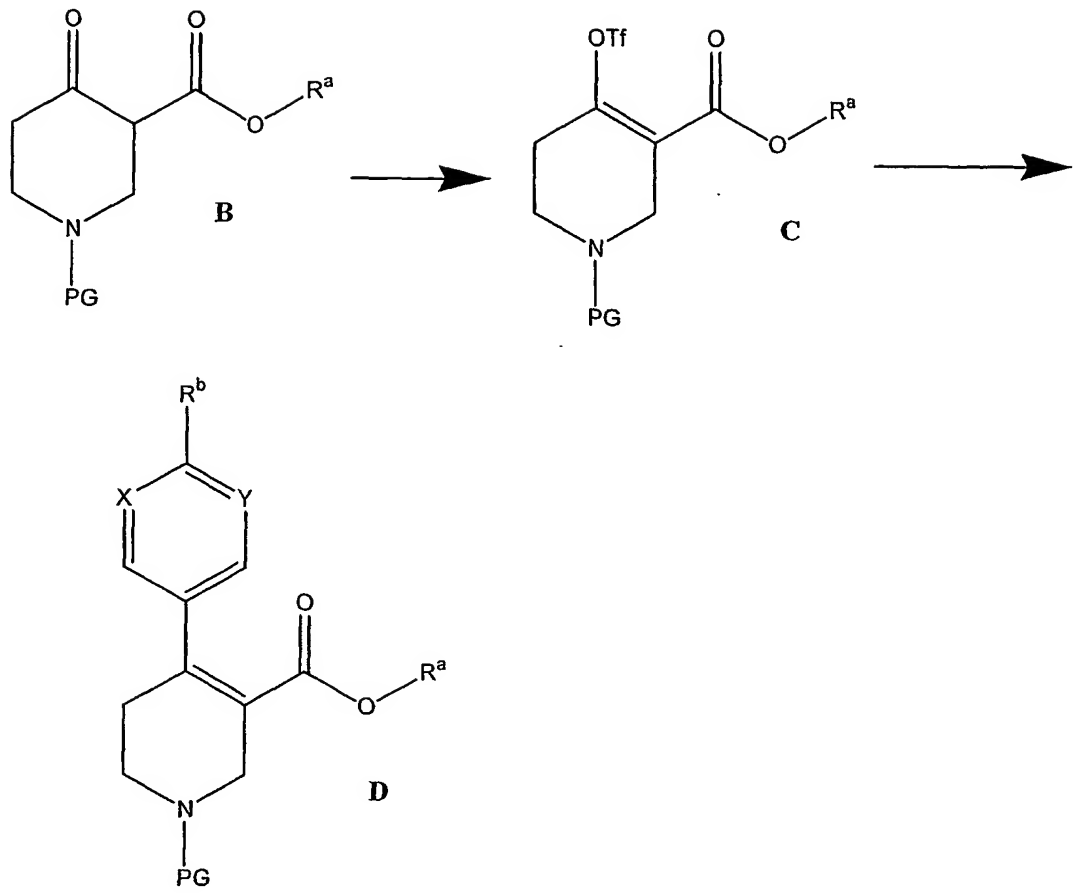
Ideal starting materials are any commercially available 4-oxo-piperidine-3-carboxylic acid ester derivatives, for instance 1-benzyl-4-oxo-piperidine-3-carboxylic acid methyl ester, possibly as a salt. For practical purposes, a transesterification (for instance according to Seebach D., *et al.*, *Synthesis*, **1982**, 138) to another ester derivative **A** (wherein R^a is optionally a lower alkyl, a lower alkenyl, or a benzyl group), thereafter a change in the *N*-protecting group (PG: all abreviations are outlined at the beginning of the chapter Examples) to a derivative of type **B**, may be necessary (Scheme 1).

Scheme 1



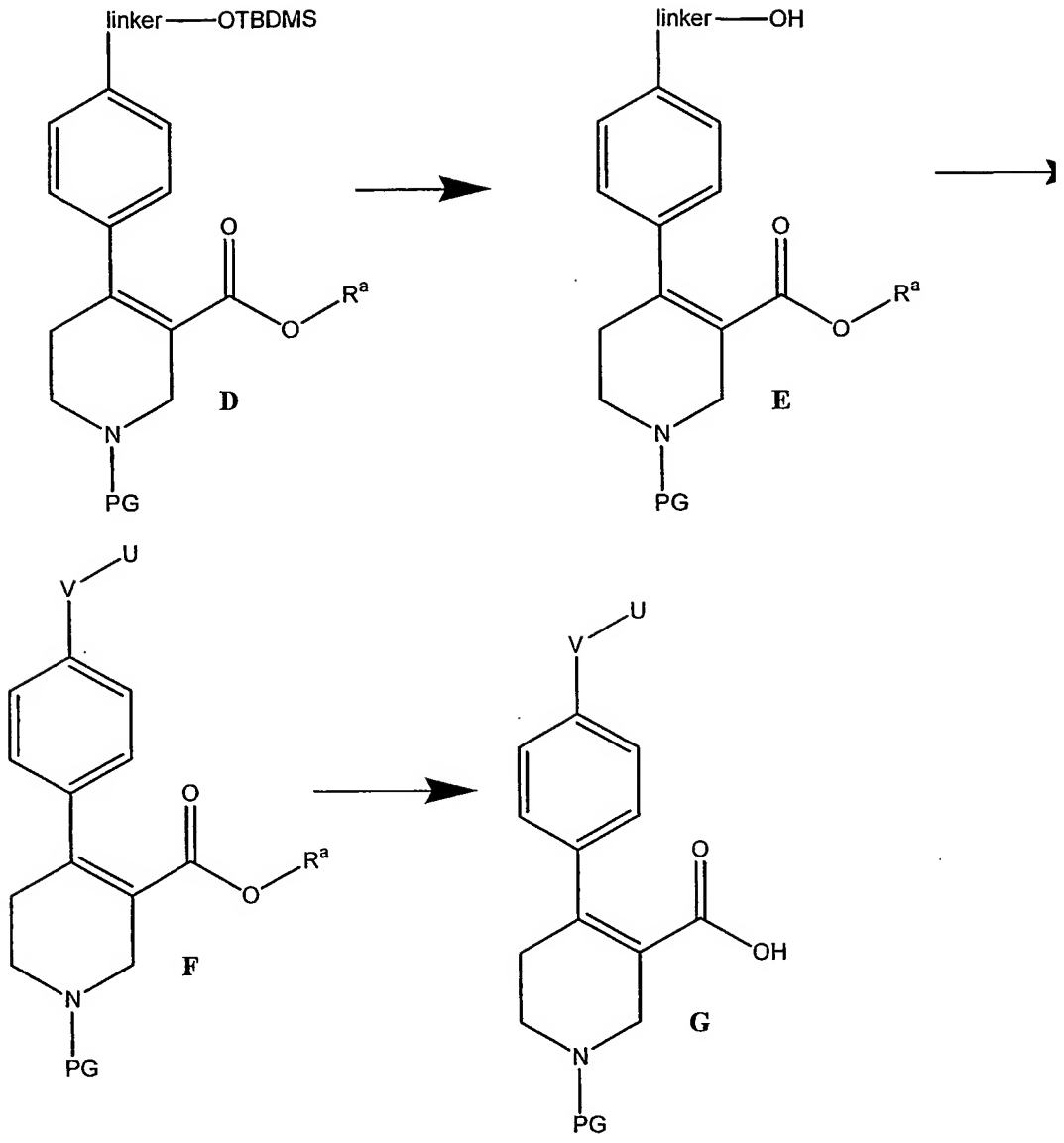
Formation of the vinyl triflate **C**, followed by a coupling catalysed by a Pd(0) complex may lead to tetrahydropyridine derivatives of type **D**, wherein R^b optionally represents any U-V group as defined in general formula **I** or a chemical precursor of such a group (Scheme 2).

Scheme 2



If, for instance, R^b is a linker ending with a silanyl ether, compounds of type **D** are deprotected to compounds of type **E**, then coupled to a phenol or aromatic alcohol using a *Mitsunobu* reaction, leading to derivatives of type **F** wherein V and U have the meaning given in general formula **I** above (Scheme 3). The ester **F** is optionally then be cleaved by any suitable method to lead to precursor **G**.

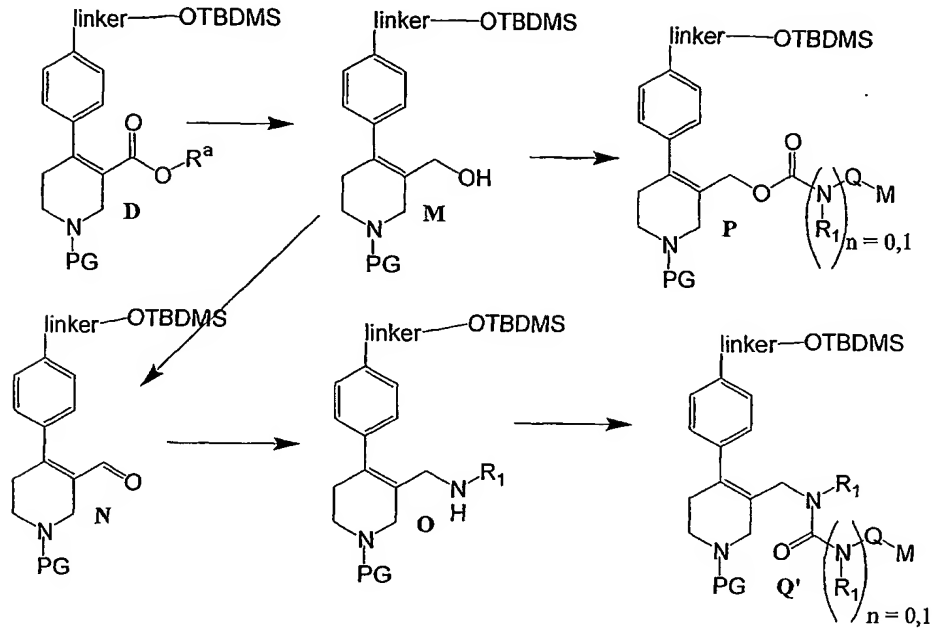
Scheme 3



Also, a compound of type **D** may be reduced with DIBAL to a compound of type **M** that can be then oxidized to a compound of type **N** with e.g. the Dess-Martin periodinane (Scheme 4). Aldehyde **N** may then be transformed to a compound of type **O** by reductive amination, which can be acylated to a derivative of type **Q'** wherein Q and M have the meaning given in general formula **I** above. On the

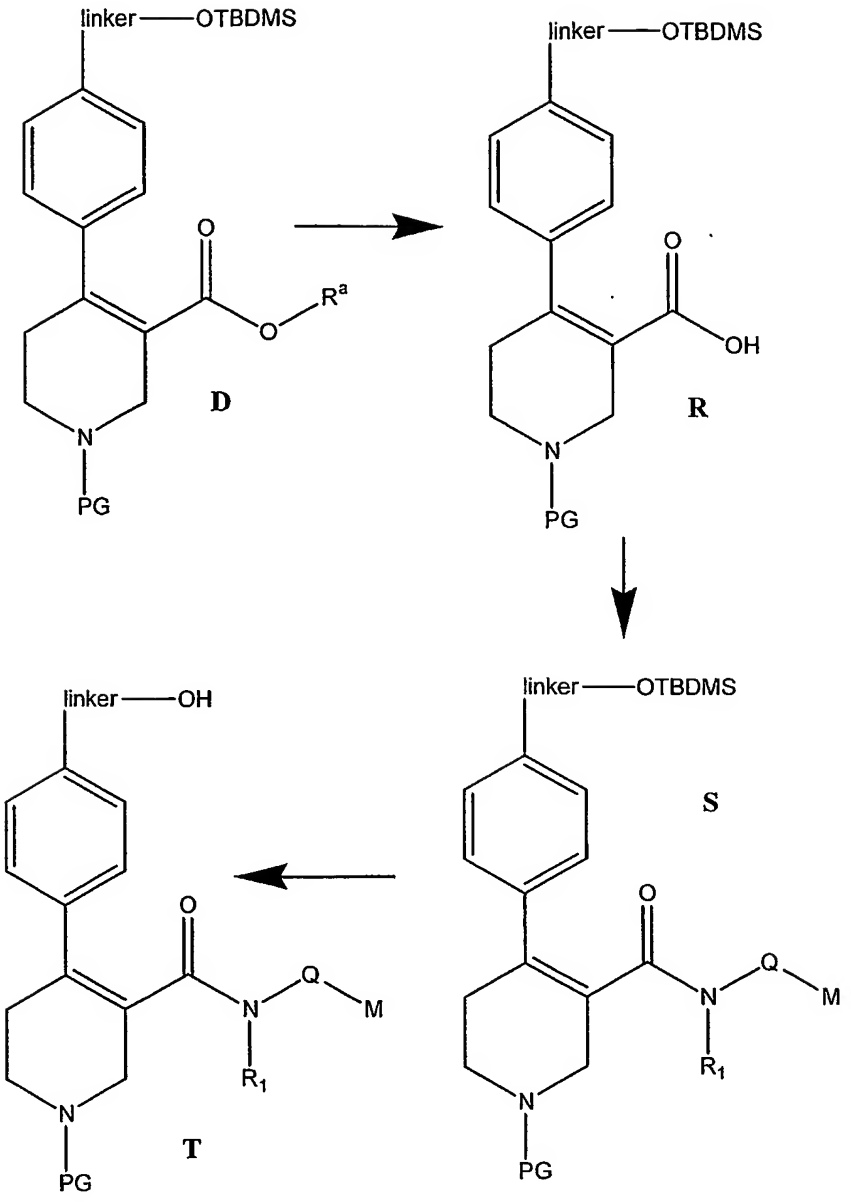
other hand, compounds of type **M** can be then acylated following standard procedures to esters or carbamates of type **P**.

Scheme 4



Also, as shown in Scheme 5, a precursor of type **T** can be prepared in three steps from a compound of type **D**, by saponification (compound of type **R**), amide coupling (compound of type **S**) and finally desilylation.

Scheme 5

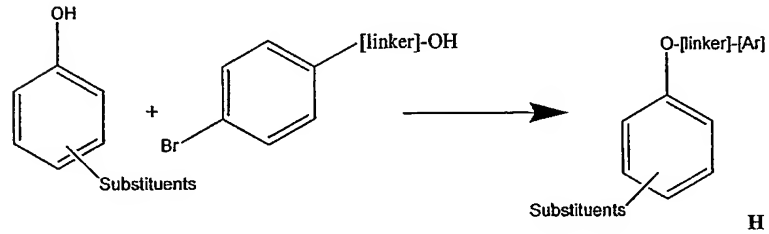


Preparation of bromoaryl derivatives

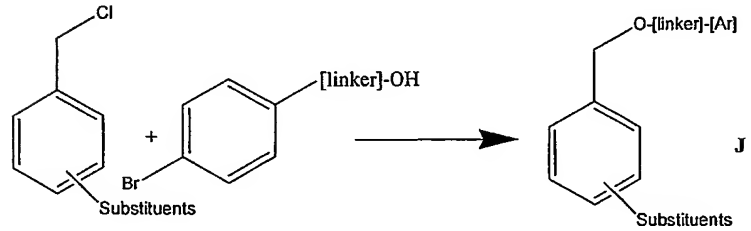
For the coupling of compounds of type **C** to tetrahydropyridine derivatives of type **D**, it can be necessary to prepare the bromoaryl components needed as described

in Scheme 6. A *Mitsunobu* coupling (→ compounds of type **H**) or the alkylation of an alcohol with a benzylic chloride (or bromide, → compounds of type **J**) are often the most convenient methods. Derivative **K** was prepared in one step from 1-(3-chloropropoxymethyl)-2-methoxybenzene by reaction with 4-bromophenol (Vieira E. *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397). Other methods for the preparation of ethers or thioethers, like a *Williamson* synthesis, might be used as well (see e.g. March, J, "Advanced Organic Chemistry", 5th ed., John Wiley and sons, 2001).

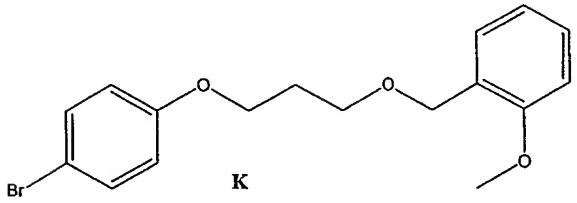
Scheme 6



H



J



K

Preparation of the secondary amines

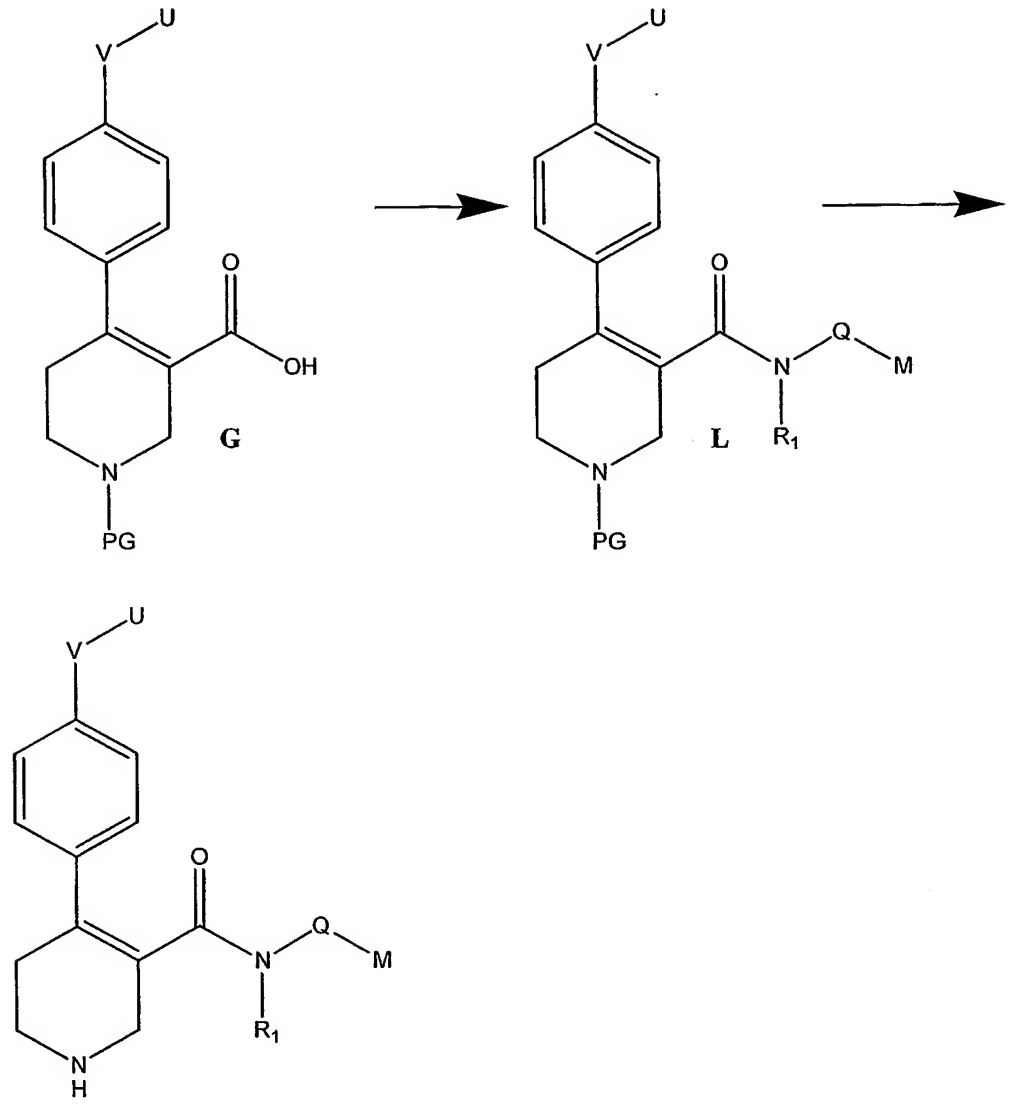
It may be necessary to prepare secondary amines as well. This can be done by reductive amination from the corresponding amine and aldehyde, or by amide

coupling, from the corresponding amine and carboxylic acid, followed by reduction with LAH or borane. These standard procedures are well-described in the literature.

Preparation of final compounds

A compound of type **G** can be coupled to the amine to yield amides of type **L** wherein V, U and M have the meaning given in general formula **I** above. Removal of the *N*-protecting group (PG) leads to a final compound, wherein V, U, Q and M have the meaning given in general formula **I** above (Scheme 7).

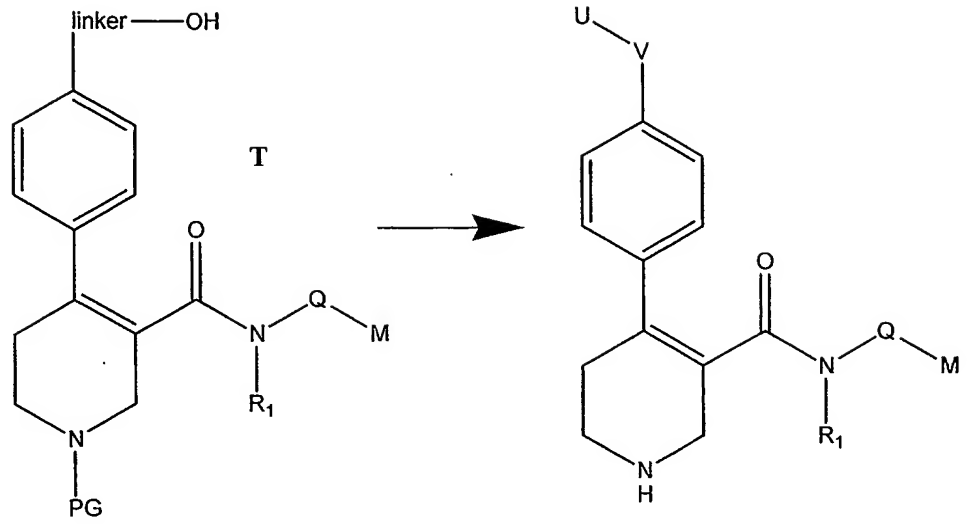
Scheme 7



Also, compounds of type **P** or **Q'** (Scheme 4) may be processed further as indicated in Scheme 3, then deprotected as indicated in Scheme 7, to lead to final compounds as defined in general formula **I**.

From a precursor of type **T** a final compound can be prepared by a *Mitsunobu*-type reaction, followed by deprotection (Scheme 8).

Scheme 8



The compounds of formula **I** and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula **I** and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants in a manner known per se.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof,

talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula **I** can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration. For children the dosage has to be adapted to the body weight and age.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula **I**.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

General remarks

The following compounds were prepared according to the procedures described for the synthesis of compounds encompassed by the general formula **I**. All compounds were characterized by ^{1}H-NMR (300 MHz) and occasionally by ^{13}C-NMR (75 MHz) (Varian Oxford, 300 MHz), by LC-MS: **A**: 2 min < t_R < 10 min; (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Column: 2x30 mm, Gromsil ODS4, 3 µM, 120A; Gradient: 0 - 100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45 mL/min; t_R given in min.), **B**: 0.1 min < t_R < 2 min; (Finnigan AQA with ESI-probe with HP 110 DAD and HP110 binary pump; column: Develosil RP-AQUEOUS, 5 µM, 4.6 mm x 50 mm; gradient: 5 - 95% methanol in water (0.04% TFA), 1 min, 95% methanol in water (0.04% TFA) 0.4 min, 4.5 mL/min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}). LC-MS- and TLC-data only are given hereby.

Abbreviations

ACE	Angiotensin Converting Enzyme
Ang	Angiotensin
aq.	aqueous
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
BuLi	*n*-Butyllithium
conc.	Concentrated
DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide

DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
eq.	equivalent
Et	Ethyl
EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol
LAH	Lithium aluminium hydride
MeOH	Methanol
org.	organic
PBS	Phosphate Buffer Saline
PG	protecting group
Ph	Phenyl
RAS	Renin Angiotensin System
RP18	Reversed phase column, filled with C_{18} hydrocarbon
rt	room temperature
sol.	Solution
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMAD	*N,N,N',N'*-Tetramethylazodicarboxamide

General procedures

General procedure A for amide coupling

A sol. of the desired carboxylic acid (1.00 eq), the desired amine (2.00 eq), EDC·HCl (1.10 eq.), HOBt (cat. amount), DMAP (cat. amount) and DIPEA (2.00 eq.) in CH_2Cl_2 (20 mL/g of acid) was stirred at rt overnight. The reaction mixture

was either washed over diatomic earth (Isolute Sorbent Technology, Johnson, C. R., *et al.*, Tetrahedron, **1998**, *54*, 4097), or washed with aq. 1M HCl, and the org. extracts were evaporated under reduced pressure. The residue was used without further purification.

General procedure B for the removal of a Boc-protecting group

The starting material was dissolved in CH_2Cl_2 (10 mL/g of starting material) and the sol. was cooled to 0 °C. 4M HCl in dioxane (same volume as CH_2Cl_2) was added and the reaction mixture was left for 90 min at rt. The solvents were removed under reduced pressure. Purification of the residue by HPLC led to the desired compound.

Typical procedure C for amide formation from acid chlorides

To a sol. of the acid chloride (1 eq.) in CH_2Cl_2 (2.5 mL/mmol) at 0 °C. the amine (3 eq.) was added. The mixture was stirred for 3 h while warming up slowly to rt. If necessary, more CH_2Cl_2 was added, then the reaction mixture was washed with aq. sat. $NaHCO_3$ (1x) and aq. 1M HCl (1x). The extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The obtained product was used without further purification.

Typical procedure D for the reduction of an amide to an amine with LAH

To a sol. of the amide (1 eq.) was dissolved in THF (3 mL/mmol) LAH (1M in THF, 3 eq.) was added carefully. The mixture was stirred at rt for 30 min, then heated to 60 °C for 3 h before it was allowed to cool down to rt, then to 0 °C. For x g of LAH initially added, was added x g of water, then x g of aq. 15% NaOH, and finally 3x g of water again. The resulting mixture was stirred overnight, filtered, and the precipitate washed with EtOAc. The filtrate was evaporated under reduced pressure and the residue diluted in a small amount of MeOH. The sol. was passed through a pad of SCX silica gel (sulfonic acid). Elution started

with MeOH, followed by NH_3/MeOH. The amines eluted with the second second eluent. The solvents were removed under reduced pressure. The isolated amines were either used without further purification or purified by HPLC, depending on the purity.

Typical procedure E for reductive amination

To a solution of aldehyde (1eq.) in MeOH (0.5 mL/mmol) was added an amine (1.2 eq.). The solution was stirred for 2h. Sodium borohydride (1.2 eq.) was added portionwise at 0°C and then stirring was continued, at rt, for 4h. A solution of NaOH 1N was added and the MeOH was evaporated. The mixture was extracted with EtOAc twice and the organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The isolated amines were either used without further purification or purified by flash chromatography (EtOAc/heptane: 2/8), depending on the purity.

Preparation of the secondary amines

(2-Chlorobenzyl)cyclopropylamine

Synthesized according to typical procedures C and D from 2-chlorobenzoyl chloride and cyclopropylamine.

(2-Chlorobenzyl)ethylamine

See Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225.

Cyclopropyl-(3,5-dimethoxybenzyl)amine

Synthesized according to typical procedure E from 2,5-dimethoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(2-fluoro-5-methoxybenzyl)amine

Synthesized according to typical procedure E from 2-fluoro-5-methoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-methoxybenzyl)amine

Synthesized according to typical procedure E from 3-methoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(3,4-dimethoxybenzyl)amine

Synthesized according to typical procedure E from 3,4-dimethoxybenzaldehyde and cyclopropylamine.

(2-Chloro-3-trifluoromethylbenzyl)cyclopropylamine

Synthesized according to typical procedure E from 2-chloro-3-trifluoromethylbenzaldehyde and cyclopropylamine.

(6-Chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamine

Synthesized according to typical procedure E from 6-chlorobenzo[1,3]dioxole-5-carbaldehyde and cyclopropylamine.

(2-Bromobenzyl)cyclopropylamine

Synthesized according to typical procedure E from 2-bromobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2,3-dimethylbenzyl)amine

Synthesized according to typical procedure E from 2,3-dimethylbenzaldehyde and cyclopropylamine.

Cyclopropyl-(3,5-difluorobenzyl)amine

Synthesized according to typical procedure E from 3,5-difluorobenzaldehyde and cyclopropylamine.

(2,3-Dichlorobenzyl)cyclopropylamine

Synthesized according to typical procedure E from 2,3-dichlorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-trifluoromethoxybenzyl)amine

Synthesized according to typical procedure E from 3-trifluoromethoxy-benzaldehyde and cyclopropylamine.

Cyclopropyl-(3-methylbenzyl)amine

Synthesized according to typical procedure E from 3-methylbenzaldehyde and cyclopropylamine.

(3-Chlorobenzyl)cyclopropylamine

Synthesized according to typical procedure E from 3-chlorobenzaldehyde and cyclopropylamine.

Cyclopropyl(2-fluorobenzyl)amine

Synthesized according to typical procedure E from 2-fluorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2-methylbenzyl)amine

Synthesized according to typical procedure E from 2-methylbenzaldehyde and cyclopropylamine.

Cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (4-methoxyphenoxy)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (3-methoxyphenoxy)-acetic acid and cyclopropylamine.

Cyclopropyl-(2-*m*-tolyloxyethyl)amine

Synthesized according to typical procedures C and D from *m*-tolylacetic acid and cyclopropylamine.

[2-(2-Chlorophenyl)ethyl]cyclopropylamine

Synthesized according to typical procedures C and D from (2-chlorophenyl)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(4-fluorophenyl)ethyl]amine

Synthesized according to typical procedures C and D from (4-fluorophenyl)acetic acid and cyclopropylamine.

Cyclopropyl-(2-*o*-tolylethyl)amine

Synthesized according to typical procedures C and D from *o*-tolylacetic acid and cyclopropylamine.

Cyclopropyl-(2-*p*-tolylethyl)amine

Synthesized according to typical procedures C and D from *p*-tolylacetic acid and cyclopropylamine.

Preparation of the precursors

4-Oxopiperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (B)

A suspension of 1-benzyl-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride (5.00 g, 17.6 mmol), triethylamine (2.45 mL, 17.6 mmol) and Boc_2O (4.20 g, 20.0 mmol) in EtOH (30 mL) was purged with N_2. Pd/C (10%, 600 mg) was added and the suspension purged with H_2. The reaction mixture was stirred under an H_2-atmosphere for 24 h and then filtered through *Celite*. The filtrate was evaporated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3) yielded the title compound (4.02 g, 89%). $R_f = 0.60$ (EtOAc/heptane 1:1). LC-MS: $R_t = 1.09$ min, ES+ = 202.03.

Compounds of type C

1-Benzyl-4-trifluoromethanesulfonyloxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester (C1)

To a suspension of 1-benzyl-4-oxo-piperidine-3-carboxylic acid ethyl ester hydrochloride (1.50 g, 5.04 mmol) in THF (30 mL) NaH (about 60% in oil, 600 mg, about 15 mmol) was added at 0°C. As the suspension turned thick CH_2Cl_2 (20 mL) was added. The ice bath was removed and Tf_2NPh (2.68 g, 7.50 mmol) was added. The mixture was stirred overnight and ice was added. The mixture was washed with aq. 10% Na_2CO_3 (1x) and the org. extracts were dried over $MgSO_4$

and filtered. The solvents were removed under reduced pressure and purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 2:3) yielded the title compound (2.10 g, almost quantitative yield). R_f = 0.50 (EtOAc/heptane 1:1). LC-MS: R_t = 4.65 min, ES+: 394.12.

4-Trifluoromethanesulfonyloxy-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (C2)

To a sol. of compound **B** (4.00 g, 15.6 mmol) in THF (100 mL) at 0 °C was added NaH (suspension in oil, 55-65%, 1.20 g, about 31 mmol). The suspension was stirred for 30 min at 0 °C and Tf_2NPh (8.27 g, 23.1 mmol) was added. The ice bath was removed and the reaction mixture stirred for 3 days at rt. Ice was added and the solvents were removed under reduced pressure. The residue was diluted with EtOAc and washed with aq. 10% Na_2CO_3. The org. extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4) yielded the title compound (5.19 g, 86%). LC-MS: R_t = 1.17, ES+ = 374.96.

Compounds of type D

1-Benzyl-4-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (D1)

To a sol. of 4-bromo-1-[3-(2-methoxybenzyloxy)propoxy]benzene (2.81 g, 8.01 mmol) in THF (50 mL) at -78 °C *n*-BuLi (1.5M in hexane, 5.60 mL, 8.41 mmol) was added. After 30 min $ZnCl_2$ (1M in THF, 9.00 mL, 9.00 mmol) was added and the mixture was allowed to warm up to rt. Vinyl triflate **C1** (2.10 g, 5.34 mmol) and $Pd(PPh_3)_4$ (154 mg, 0.134 mmol) were added and the mixture stirred at rt for 4.5 h. Ice was added, the mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC

(EtOAc/heptane 1:9 → 1:4 → 2:3 → 3:2) led to the title compound (2.25 g, 82%). R_f = 0.32 (EtOAc/heptane 1:1). LC-MS: R_t = 4.05 min, ES+ = 516.23.

4-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (D2)

To a sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183; 6.19 g, 19.7 mmol) in THF (100 mL) at -78 °C was added n-BuLi (1.5M in hexane, 14.0 mL, 21.0 mmol). The sol. was stirred at -78 °C for 30 min and $ZnCl_2$ (1M in THF, 22.3 mL, 22.3 mmol) was added. The resulting sol. was allowed to warm to rt and compound **C2** (5.10 g, 13.1 mmol) and $Pd(PPh_3)_4$ (300 mg, 0.26 mmol) were added. After 20 min at rt ice was added to the reaction mixture. The solvents were removed under reduced pressure and the residue diluted with EtOAc. This mixture was washed with aq. 1M NaOH. The org. extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9) led to the title compound (5.77 g, 90%). LC-MS: R_t = 7.27 min, ES+ = 512.54.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (D3)

As described for compound **D2** but from [2-(4-bromo-phenoxy)ethoxy]-*tert*-butyldimethylsilane (Morita, C.; et al.al.; *Heterocycles*, **2000**, *52*, 1163; 49.5 g, 149 mmol), BuLi (1.6M in hexane, 94 mL, 150 mmol), $ZnCl_2$ (1M in THF, 200 mL, 200 mmol), compound **C2** (37.0 g, 95 mmol), $Pd(PPh_3)_4$ (2.75 g, 2.38 mmol) and THF (750 mL). Purification by FC yielded the title compound (36.6 g, 78%). LC-MS: R_t = 1.20 min, ES+ = 492.34.

Compounds of type E

4-[4-(3-Hydroxypropyl)phenyl]-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (E1)

TBAF (1.90 g, 6.00 mmol) was added to a sol. of compound **D2** (1.95 g, 4.00 mmol) in THF (40 mL). The reaction mixture was stirred for 6 h at rt and diluted with EtOAc. The resulting mixture was washed with water and brine. The org. extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) yielded the title compound (1.27 g, 84%). LC-MS: R_t = 1.06, ES+ = 376.18.

4-[4-(2-Hydroxyethoxy)phenyl]-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester-3-methyl ester (E2)

As described for compound **E1** but from compound **D3** (5.63 g, 11.4 mmol), TBAF (5.41 g, 17.1 mmol) and THF (115 mL). Purification by FC yielded the title compound (3.46 g, 80%). LC-MS: R_t = 1.01; ES+ = 378.22.

Compounds of type F

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F1)

A sol. of compound **E1** (750 mg, 2.00 mmol), 2-bromo-5-fluorophenol (0.334 mL, 3.00 mmol), azodicarboxyl dipiperidide (757 mg, 3.00 mmol), tri-n-butylphosphine (0.987 mL, 4.00 mmol) and DIPEA (0.035 mL, 0.20 mmoL) in toluene (20 mL) was stirred for 1 h at rt, then for 2 h at 60 °C. The reaction mixture was allowed to cool to rt, was diluted with EtOAc and washed with water. The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7) led to the title compound (898 mg, 82%). LC-MS: R_t = 6.43 min, ES+ = 570.00.

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F2)

A sol. of compound **E1** (375 mg, 1.00 mmol), 2-chlorophenol (0.153 mL, 1.50 mmol), azodicarboxyl dipiperidide (378 mg, 1.50 mmol), tri-n-butylphosphine (0.493 mL, 2.00 mmol) and DIPEA (0.018 mL, 0.10 mmoL) in toluene (10 mL) was stirred for 1 h at rt, then for 2 h at 60 °C. The reaction mixture was allowed to cool to rt, was diluted with EtOAc and washed with water. The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7) led to the title compound (374 mg, 77%). LC-MS: R_t = 1.39 min, ES+ = 486.13.

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F3)

A sol. of compound **E1** (375 mg, 1.00 mmol), 2,5-difluorophenol (195 mg, 1.50 mmol), azodicarboxyl dipiperidide (378 mg, 1.50 mmol), tri-n-butylphosphine (0.493 mL, 2.00 mmol) and DIPEA (0.018 mL, 0.10 mmoL) in toluene (10 mL) was stirred for 1 h at rt, then for 2 h at 60 °C. The reaction mixture was allowed to cool to rt, was diluted with EtOAc and washed with water. The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7) led to the title compound (378 mg, 77%). LC-MS: R_t = 1.35 min, ES+ = 488.16.

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F4)

Prepared as described for compound **F1** but from compound **E1** (4.7 g, 12.5 mmol), 2,3,6-trifluorophenol (3.7 g, 25.0 mmol), azodicarboxyl dipiperidide (6.32 g, 34.2 mmol), tributylphosphine (85%, 9.3 mL, 37.6 mmol) and toluene (100 mL). Purification of the residue by FC yielded the title compound (5.23 g, 83%).

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F5)

As described for compound **D2** but from compound **H1** (3.07 g, 9.63 mmol), BuLi (1.6M in hexane, 6.9 mL, 10.3 mmol), $ZnCl_2$ (1M in THF, 10.9 mL, 10.9 mmol), compound **C2** (2.50 g, 6.42 mmol), $Pd(PPh_3)_4$ (148 mg, 0.128 mmol) and THF (50 mL). Purification by FC yielded the title compound (1.77 g, 57%).

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F6)

Prepared as described for compound **F1** but from compound **E2** (1.69 g, 4.4 mmol), 2-chloro-4,5-dimethylphenol (1.05 g, 6.6 mmol), azodicarboxyl dipiperidide (1.67 g, 6.6 mmol), tributylphosphine (2.2 mL, 8.8 mmol) and toluene (45 mL). Purification of the residue by FC yielded the title compound (1.73 g, 76%). LC-MS: R_t = 1.38; ES+: 516.24.

Compounds of type G

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G1)

To a sol. of compound **F1** (742 mg, 1.30 mmol) in EtOH (13 mL) was added aq. 1M NaOH (13 mL). The resulting mixture was stirred for 35 min at 80 °C, then allowed to cool to rt. Aq. 1M HCl (13 mL) was added and the resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) led to the title compound (418 mg, 60%). LC-MS: R_t = 1.32 min, ES+ = 534.04.

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G2)

To a sol. of compound **F2** (374 mg, 0.77 mmol) in EtOH (8 mL) was added aq. 1M NaOH (7.7 mL). The resulting mixture was stirred for 35 min at 80 °C, then allowed to cool to rt. Aq. 1M HCl (7.7 mL) was added and the resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) led to the title compound (218 mg, 60%). LC-MS: R_t = 1.29 min, ES+ = 472.15.

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G3)

To a sol. of compound **F3** (378 mg, 0.77 mmol) in EtOH (8 mL) was added aq. 1M NaOH (7.7 mL). The resulting mixture was stirred for 35 min at 80 °C, then allowed to cool to rt. Aq. 1M HCl (7.7 mL) was added and the resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) led to the title compound (220 mg, 60%). LC-MS: R_t = 1.25 min, ES+ = 474.17.

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G4)

As described for compound **G1**, but from compound **F4** (5.23 g, 10.3 mmol), aq. NaOH (1M, 90 mL) and EtOH (90 mL). The title product was used further without chromatographic purification (4.55 g, 89%).

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G5)

As described for compound **G1**, but from compound **F5** (2.17 g, 4.53 mmol), aq. NaOH (1M, 30 mL) and EtOH (30 mL). The title product was used further without chromatographic purification (1.86 g, 89%).

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G6)

As described for compound **G1**, but from compound **F6** (1.73 g, 3.3 mmol), aq. NaOH (1M, 33 mL) and EtOH (33 mL). The title product was used further without chromatographic purification. LC-MS: R_t = 1.10; ES+: 502.31.

2-(4-Bromophenyl)eth-1-yl 2,3,5-trimethylphenyl ether (H1)

A mixture of 2-(4-bromophenyl)ethanol (20.0 mL, 143 mmol), 2,3,5-trimethylphenol (31.1 g, 229 mmol), azodicarboxylic dipiperidide (72.1 g, 286 mmol) and tributylphosphine (88 mL; 357 mmol) in toluene (2.00 L) was heated to reflux for 2 h. The mixture was allowed to cool to rt. The mixture was filtered, washed with toluene and the solvents were partially removed under reduced pressure. The residue was diluted with Et_2O and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (petroleum ether → Et_2O/petroleum ether 1:3) yielded the title compound (33.1 g, 73%). LC-MS: R_t = 6.95.

1-Bromo-4-[3-(2-methoxybenzyloxy)prop-1-yloxy]benzene (K)

4-Bromophenol (4.32 g, 25.0 mmol) and 1-(3-chloro-propoxymethyl)-2-methoxy-benzene (Vieira E., *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397) (4.88 g, 22.7 mmoL) were dissolved in DMF (150 mL). NaI (1.50 g, 0.10 mmol) and Cs_2CO_3 (16.3 g, 50.0 mmol) were added. The mixture was heated to 80 °C and stirred for 6 h before it was allowed to cool to rt. After dilution with EtOAc (600 mL) the mixture was washed with water (1x), aq. 1M NaOH (1x), and aq. 1M HCl

(1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (Et_2O/petroleum ether 1:9 → 1:4) yielded the title compound (5.66 g, 71%). R_f = 0.60 (Et_2O/heptane 1:1). ^{1}H-NMR ($CDCl_3$): 7.38 - 7.34 (m, 3 H); 7.26 (t, J = 8.7 Hz, 1 H); 6.94 (t, J = 8.7 Hz, 1 H); 6.86 (d, J = 8.2 Hz, 1 H); 6.78 (d, J = 9.0 Hz, 2 H); 4.57 (s, 2 H); 4.07 (t, J = 6.3 Hz, 2 H); 3.81 (s, 3 H); 3.70 (t, J = 6.3 Hz, 2 H); 2.10 (quint., J = 6.3 Hz, 2 H).

1-Benzyl-4-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide (L1)

To a suspension of tetrahydropyridine **D1** (2.25 g, 4.26 mmol) in EtOH (50 mL) NaOH (1M in water, 30 mL) was added. After 4 h the mixture was warmed up to 60 °C and stirred for 5 h. The reaction mixture was allowed to cool to rt, and the pH was adjusted to 7 with aq. 1M HCl. The solvents were removed under reduced pressure and the residue was dried at high vacuum. The dried residue was triturated with EtOH and filtered (3x), the combined filtrates were evaporated under reduced pressure, and the residue was dried at high vacuum. The residue was diluted in $CHCl_3$ (20 mL), and [2-(2-chlorophenyl)ethyl]methylamine (Jaques B.; Wallace R. G., *Tetrahedron*, **1977**, *33*, 581, 1.48 g, 8.72 mmol), DMAP (cat. amount), HOBt (cat. amount) and EDC·HCl (836 mg, 4.36 mmol) were added. After 4 h at rt the mixture was diluted with CH_2Cl_2 and washed with aq. 10% Na_2CO_3 (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3 → 3:2 → EtOAc) gave the title compound (0.48 g, 17%). R_f = 0.13 (EtOAc/heptane 1:1). LC-MS: R_t = 4.24 min, ES+ = 639.33.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (R)

A sol. of compound **D3** (17.6 g) in MeOH (400 ml) and 1N NaOH-soln. (250 ml) was heated at 110°c for 1.5 h. The mixture was allowed to cool to rt and aq. 1M HCl was added to reach pH 4, and was extracted with EtOAc (2x150 ml). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. A sol. this crude material (14g), imidazol (9.75g) and TBDMSCl (13.49g) in DMF (80 ml) was stirred at room temperature for 1h. Aq. sat. NH_4Cl (100ml) was added and the mixture was extracted with heptane (3x100ml).).The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. A sol. of this crude product, and K_2CO_3 (2.5 g) in MeOH (50 ml) and water (50 ml) was stirred at room temperature for 1h. Aq. sat. NH_4Cl (100ml) was added and the mixture was extracted with Et_2O (3x50ml).).The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude title product (17.2g, quant. yield) was used in the next step without purification. LC-MS: R_t = 1.12; ES+:478.38.

Compounds of type S

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(2-chloro-3-trifluoromethylbenzyl)cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S1)

A sol. of compound **R** (2.62 g, 5.5 mmol), (2-chloro-3-trifluoromethylbenzyl)-cyclopropylamine (2.74 g, 11.0 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL) was stirred overnight. The mixture was washed with aq. 1M HCl (3x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 1:3) yielded the title compound (2.95 g, 75%). R_f = 0.55 (EtOAc/heptane 1:1). LC-MS: R_t = 7.68.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3,5-difluorobenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S2)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(3,5-difluorobenzyl)amine (2.01 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.83 g, 79%). LC-MS: R_t = 1.20; ES+: 643.23.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S3)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(2,3-dichlorobenzyl)amine (2.38 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.02 g, 53%). LC-MS: R_t = 1.20; ES+: 675.15.

5-[(2-Bromobenzyl)cyclopropylcarbamoyl]-4-{4-[2-(*tert*-butyldimethyl-silanyloxy)ethoxy]phenyl}-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S4)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), (2-bromobenzyl)cyclopropylamine (2.49 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.02 g, 53%). LC-MS: R_t = 1.26; ES+: 687.41.

4-{4-[2-(tert-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(2,3-dimethylbenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S5)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(2,3-dimethylbenzyl-amine (1.93 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.25 g, 64%). LC-MS: R_t = 1.26; ES+: 635.53.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3-trifluoromethoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S6)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(3-trifluoromethoxybenzyl)amine (2.54 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.51 g, 66%). LC-MS: R_t = 1.26; ES+: 691.48.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3-methylbenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S7)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(3-methylbenzyl)amine (1.77 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.14 g, 62%). LC-MS: R_t = 1.25; ES+: 621.54.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(3-chlorobenzyl)-cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S8)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), (3-chlorobenzyl)cyclopropylamine (1.99 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.44 g, 69%). LC-MS: R_t = 1.26; ES+: 641.44.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(2-chlorobenzyl)-ethylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S9)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), (2-chlorobenzyl)ethylamine (1.87 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.31 g, 67%). LC-MS: R_t = 1.25; ES+: 629.45.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(2-fluoro-5-methoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S10)

As described for compound **S1**, but from compound **R** (2.59 g, 5.42 mmol), cyclopropyl-(2-fluoro-5-methoxybenzyl)amine (2.12 g, 10.8 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.70 mL, 21.7 mmol), HOBt (732 mg, 5.42 mmol) and EDC·HCl (1.56 g, 8.13 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.21 g, 62%).

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(6-chlorobenzo[1,3]-dioxol-5-ylmethyl)cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S11)

As described for compound **S1**, but from compound **R** (2.41 g, 5.05 mmol), (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamine (2.28 g, 10.1 mmol), DMAP (123 mg, 1.01 mmol), DIPEA (3.50 mL, 20.2 mmol), HOBt (682 mg, 5.05 mmol) and EDC·HCl (1.45 g, 7.58 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (1.97 g, 57%).

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S12)

As described for compound **S1**, but from compound **R** (2.80 g, 5.86 mmol), cyclopropyl-(3,5-dimethoxybenzyl)amine (2.43 g, 11.7 mmol), DMAP (143 mg, 1.17 mmol), DIPEA (3.00 mL, 17.6 mmol), HOBt (792 mg, 5.86 mmol) and EDC·HCl (1.68 g, 8.79 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.97 g, 76%). LC-MS: $R_t = 1.23$; ES+ = 667.1.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3-methoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S13)

As described for compound **S1**, but from compound **R** (2.80 g, 5.86 mmol), cyclopropyl-(3-methoxybenzyl)amine (2.08 g, 11.7 mmol), DMAP (143 mg, 1.17 mmol), DIPEA (3.00 mL, 17.6 mmol), HOBt (792 mg, 5.86 mmol) and EDC·HCl (1.68 g, 8.79 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.68 g, 72%). LC-MS: $R_t = 1.23$; ES+ = 637.3.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3,4-dimethoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S14)

As described for compound **S1**, but from compound **R** (2.48 g, 5.19 mmol), cyclopropyl-(3,4-dimethoxybenzyl)amine (2.15 g, 10.4 mmol), DMAP (127 mg, 1.04 mmol), DIPEA (3.60 mL, 20.8 mmol), HOBt (700 mg, 5.19 mmol) and EDC·HCl (1.49 g, 7.79 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.92 g, 84%). LC-MS: R_t = 1.23; ES+ = 637.3.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(2-chlorobenzyl)-cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S15)

As described for compound **S1**, but from compound **R** (3.82 g, 8.00 mmol), (2-chlorobenzyl)cyclopropylamine (4.36 g, 24.0 mmol), DMAP (195 mg, 1.60 mmol), DIPEA (5.50 mL, 32.0 mmol), HOBt (1.08 g, 8.00 mmol) and EDC·HCl (2.30 g, 12.0 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (3.10 g, 60%). LC-MS: R_t = 1.26; ES+ = 641.4.

Compounds of type T

5-[(2-Chloro-3-trifluoromethylbenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T1)

A sol. of compound **S1** (2.95 g, 4.16 mmol) and TBAF (1M in THF, 6.24 mL, 6.24 mmol) in THF (15 mL) was stirred at rt for 90 min. The mixture was diluted with EtOAc and washed with brine (1x), water (1x) and brine again (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 →

3:2 → 4:1) yielded the title compound (1.56 g, 63%). R_f = 0.10 (EtOAc/heptane 1:1) were collected. LC-MS: R_t = 5.63; ES+ = 595.37.

5-[Cyclopropyl-(3,5-difluorobenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T2)

As described for compound **T1**, but from compound **S2** (2.83 g, 4.40 mmol), TBAF (1M in THF, 6.60 mL, 6.60 mmol) and THF (15 mL). Purification by FC yielded the title compound (0.95 g, 41%). LC-MS: R_t = 5.16; ES+ = 529.48.

5-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T3)

As described for compound **T1**, but from compound **S3** (2.47 g, 3.66 mmol), TBAF (1M in THF, 5.48 mL, 5.48 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.43 g, 70%). LC-MS: R_t = 5.52; ES+ = 561.31.

5-[(2-Bromobenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T4)

As described for compound **T1**, but from compound **S4** (2.02 g, 2.95 mmol), TBAF (1M in THF, 4.42 mL, 4.42 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.40 g, 83%). LC-MS: R_t = 5.22; ES+ = 571.32.

5-[Cyclopropyl-(2,3-dimethylbenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T5)

As described for compound **T1**, but from compound **S5** (2.25 g, 3.54 mmol), TBAF (1M in THF, 5.32 mL, 5.32 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.74 g, 94%). LC-MS: R_t = 5.32; ES+ = 521.68.

5-[Cyclopropyl-(3-trifluoromethoxybenzyl)carbamoyl]-4-[4-(2-hydroxy-ethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T6)

As described for compound **T1**, but from compound **S6** (2.51 g, 3.63 mmol), TBAF (1M in THF, 5.45 mL, 5.45 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.94 g, 93%). LC-MS: R_t = 1.04; ES+ = 577.32.

5-[Cyclopropyl-(3-methylbenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T7)

As described for compound **T1**, but from compound **S7** (2.14 g, 3.45 mmol), TBAF (1M in THF, 5.20 mL, 5.20 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.66 g, 95%). LC-MS: R_t = 5.19; ES+ = 507.58.

5-[(3-Chlorobenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T8)

As described for compound **T1**, but from compound **S8** (2.44 g, 3.80 mmol), TBAF (1M in THF, 5.70 mL, 5.70 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.71 g, 85%). LC-MS: R_t = 5.25; ES+ = 527.37.

5-[(2-Chlorobenzyl)ethylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T9)

As described for compound **T1**, but from compound **S9** (2.31 g, 3.67 mmol), TBAF (1M in THF, 5.50 mL, 5.50 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.40 g, 74%). LC-MS: R_t = 5.19; ES+ = 559.06.

5-[Cyclopropyl-(2-fluoro-5-methoxybenzyl)carbamoyl]-4-[4-(2-hydroxy-ethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T10)

As described for compound **T1**, but from compound **S10** (1.97 g, 2.87 mmol), TBAF (1M in THF, 5.75 mL, 5.75 mmol) and THF (20 mL). Purification by FC yielded the title compound (1.50 g, 97%). LC-MS: R_t = 5.02; ES+ = 541.46.

5-[(6-Chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T11)

As described for compound **T1**, but from compound **S11** (2.20 g, 3.37 mmol), TBAF (1M in THF, 6.75 mL, 6.75 mmol) and THF (25 mL). Purification by FC yielded the title compound (1.58 g, 82%). LC-MS: R_t = 5.28; ES+ = 571.34.

5-[Cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T12)

As described for compound **T1**, but from compound **S12** (2.97 g, 4.45 mmol), TBAF (1M in THF, 8.90 mL, 8.90 mmol) and THF (30 mL). Purification by FC yielded the title compound (2.14 g, 87%). LC-MS: R_t = 0.99; ES+ = 553.2.

5-[Cyclopropyl-(3-methoxybenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T13)

As described for compound **T1**, but from compound **S13** (2.68 g, 4.21 mmol), TBAF (1M in THF, 8.40 mL, 8.40 mmol) and THF (30 mL). Purification by FC yielded the title compound (2.03 g, 92%). LC-MS: R_t = 0.97; ES+ = 523.2.

5-[Cyclopropyl-(3,4-dimethoxybenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T14)

As described for compound **T1**, but from compound **S14** (2.92 g, 4.38 mmol), TBAF (1M in THF, 8.80 mL, 8.80 mmol) and THF (30 mL). Purification by FC yielded the title compound (2.02 g, 83%). LC-MS: R_t = 0.96; ES+ = 553.21.

5-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T15)

As described for compound **T1**, but from compound **S15** (3.10 g, 4.84 mmol), TBAF (1M in THF, 10.3 mL, 10.3 mmol) and THF (40 mL). Purification by FC yielded the title compound (2.35 g, 92%). LC-MS: R_t = 1.02; ES+ = 527.14.

Preparation of the final compounds

Example 1

4-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide trifluoroacetate salt

To a sol. of tetrahydropyridine **L1** (410 mg, 0.641 mmol) in CH_2ClCH_2Cl (10 mL) at rt $ClCO_2CHClCH_3$ (0.350 mL, 3.21 mmol) was added. The sol. was stirred at rt for 1 h, then heated to reflux. After 5 h another portion of $ClCO_2CHClCH_3$ (0.350 mL, 3.21 mmol) was added. After 1 h the solvents were removed under reduced pressure, and the residue was diluted with MeOH (5 mL) and water (5 mL). The mixture was stirred overnight and the solvents were partially removed under reduced pressure. The residue was diluted with EtOAc and the mixture was washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by HPLC (H_2O, MeOH, TFA) yielded the title compound (31 mg). LC-MS: R_t = 3.98 min, ES+ = 593.13.

Example 2

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and [2-(2-chlorophenyl)ethyl]methylamine (Jaques, B.; Wallace, R. G., *Tetrahedron*, **1977**, *33*, 581). LC-MS: R_t = 1.04 min, ES+ = 586.96.

Example 3

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and methylphenethylamine. LC-MS: R_t = 1.01 min, ES+ = 553.01.

Example 4

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and (2-chlorobenzyl)methylamine (Holzgrabe, U.; *Arch. Pharm. (Weinheim, Ger.)*, **1987**, *320*, 647). LC-MS: R_t = 1.03 min, ES+ = 572.95.

Example 5

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and (2-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 1.07 min, ES+ = 598.98.

Example 6

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide formate salt

According to the general procedures A and B, starting from compound **G2** and [2-(2-chlorophenyl)ethyl]methylamine (Jaques, B.; Wallace, R. G., *Tetrahedron*, **1977**, *33*, 581). LC-MS: R_t = 0.99 min, ES+ = 523.02.

Example 7

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide formate salt

According to the general procedures A and B, starting from compound **G2** and methylphenethylamine. LC-MS: R_t = 0.96 min, ES+ = 489.07.

Example 8

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide formate salt

According to the general procedures A and B, starting from compound **G2** and (2-chlorobenzyl)methylamine (Holzgrabe, U.; *Arch. Pharm. (Weinheim, Ger.)*, **1987**, *320*, 647). LC-MS: R_t = 0.98 min, ES+ = 509.01.

Example 9

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G2** and (2-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 1.02 min, ES+ = 535.06.

Example 10

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide formate salt

According to the general procedures A and B, starting from compound **G3** and [2-(2-chlorophenyl)ethyl]methylamine (Jaques, B.; Wallace, R. G., *Tetrahedron*, **1977**, *33*, 581). LC-MS: R_t = 0.97 min, ES+ = 525.03.

Example 11

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide formate salt

According to the general procedures A and B, starting from compound **G3** and methylphenethylamine. LC-MS: R_t = 0.94 min, ES+ = 491.10.

Example 12

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide formate salt

According to the general procedures A and B, starting from compound **G3** and (2-chlorobenzyl)methylamine (Holzgrabe, U.; *Arch. Pharm. (Weinheim, Ger.)*, **1987**, *320*, 647). LC-MS: R_t = 0.96 min, ES+ = 511.01.

Example 13

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G3** and (2-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 1.00 min, ES+ = 537.03.

Example 14

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and (2-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 1.07 min, ES+ = 598.98.

Example 15

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and (2-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 1.03 min, ES+ = 555.17.

Example 16

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and (2-chlorobenzyl)ethylamine. LC-MS: R_t = 1.01 min, ES+ = 543.16.

Example 17

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluorobenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2-fluorobenzyl)amine. LC-MS: R_t = 1.01 min, ES+ = 539.14.

Example 18

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(3-trifluoromethoxybenzyl)amine. LC-MS: R_t = 1.04 min, ES+ = 589.14.

Example 19

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2-methylbenzyl)amine. LC-MS: R_t = 1.03 min, ES+ = 535.17.

Example 20

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine. LC-MS: R_t = 1.00 min, ES+ = 581.33.

Example 21

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amine. LC-MS: R_t = 1.02 min, ES+ = 581.34.

Example 22

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*m*-tolyloxyethyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2-*m*-tolyloxyethyl)amine. LC-MS: R_t = 1.05 min, ES+ = 565.31.

Example 23

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]cyclopropylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and [2-(2-chlorophenyl)ethyl]cyclopropylamine. LC-MS: R_t = 0.93 min, ES+ = 569.41.

Example 24

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-fluorophenyl)ethyl]amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-[2-(4-fluorophenyl)ethyl]amine. LC-MS: R_t = 0.92 min, ES+ = 553.51.

Example 25

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*o*-tolylethyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2-*o*-tolylethyl)amine. LC-MS: R_t = 0.93 min, ES+ = 549.47.

Example 26

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(3,5-dimethoxybenzyl)amine. LC-MS: R_t = 0.91 min, ES+ = 581.48.

Example 27

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl(2-p-tolylethyl)amine. LC-MS: R_t = 0.93 min, ES+ = 549.53.

Example 28

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethylbenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G5** and cyclopropyl-(3-trifluoromethylbenzyl)amine LC-MS: R_t =0.96 min, ES+ = 563.46.

Example 29

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G5** and cyclopropyl-(2-methylbenzyl)amine. LC-MS: R_t =0.94 min, ES+ = 509.50.

Example 30

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropylphenethylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G5** and cyclopropylphenethylamine. LC-MS: R_t = 0.94 min, ES+ = 509.53.

Example 31

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and (2-chlorobenzyl)ethylamine. LC-MS: R_t = 0.92 min, ES+ = 587.13.

Example 32

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and cyclopropyl-(2-methylbenzyl)amine. LC-MS: R_t = 0.92 min, ES+ = 577.20.

Example 33

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine. LC-MS: R_t = 0.91 min, ES+ = 623.21.

Example 34

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropylphenethylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and cyclopropylphenethylamine. LC-MS: R_t = 0.92 min, ES+ = 577.19.

Example 35

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-*o*-tolylethyl)amide

According to the general procedures A and B, starting from compound **G1** and cyclopropyl-(2-*o*-tolylethyl)amine. LC-MS: R_t = 0.93 min, ES+ = 593.19.

Example 36

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and cyclopropyl-(3,5-dimethoxybenzyl)amine. LC-MS: R_t = 0.90 min, ES+ = 623.38.

Example 37

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and cyclopropyl-(2-*p*-tolylethyl)amine. LC-MS: R_t = 0.95 min, ES+ = 591.38.

Example 38

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G6** and (2-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 0.92 min, ES+ = 577.20.

Example 39

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2-fluoro-5-methoxybenzyl)amine. LC-MS: R_t = 0.91 min, ES+ = 569.16.

Example 40

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(3-methoxybenzyl)amine. LC-MS: R_t = 0.91 min, ES+ = 551.17.

Example 41

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,4-dimethoxybenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(3,4-dimethoxybenzyl)amine. LC-MS: R_t = 0.88 min, ES+ = 581.18.

Example 42

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G4** and (2-chloro-3-trifluoromethylbenzyl)cyclopropylamine. LC-MS: R_t = 0.96 min, ES+ = 623.07.

Example 43

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G4** and (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamine. LC-MS: R_t = 0.93 min, ES+ = 599.08.

Example 44

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-6-fluorobenzyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G4** and (2-chloro-6-fluorobenzyl)-cyclopropylamine. LC-MS: R_t = 0.92 min, ES+ = 573.10.

Example 45

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G4** and (2-bromobenzyl)cyclopropylamine. LC-MS: R_t = 0.94 min, ES+ = 601.04.

Example 46

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2,3-dimethylbenzyl)amine. LC-MS: R_t = 0.94 min, ES+ = 549.17.

Example 47

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-fluoro-2-methylbenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(3-fluoro-2-methylbenzyl)amine. LC-MS: R_t = 0.93 min, ES+ = 553.17.

Example 48

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2,3-dichlorobenzyl)amine. LC-MS: R_t = 0.95 min, ES+ = 589.07.

Example 49

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methylbenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(3-methylbenzyl)amine. LC-MS: R_t = 0.93 min, ES+ = 535.19.

Example 50

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-difluorobenzyl)amide formate salt

According to the general procedures A and B, starting from compound **G4** and cyclopropyl-(2,3-difluorobenzyl)amine. LC-MS: R_t = 0.92 min, ES+ = 557.15.

Example 51

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures A and B, starting from compound **G4** and (3-chlorobenzyl)cyclopropylamine. LC-MS: R_t = 0.93 min, ES+ = 555.07.

Example 52

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.97 min, ES+ =620.90.

Example 53

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** (50 mg) and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.98 min, ES+ =653.03.

Example 54

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.96 min, ES+ =579.12.

Example 55

4-{4-[2-(2,3,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T1** and 2,3,6-trifluorophenol. LC-MS: R_t =0.94 min, ES+ =625.20.

Example 56

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.94 min, ES+ =635.19.

Example 57

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,4,6-trifluorophenol. LC-MS: R_t =0.93 min, ES+ =591.16.

Example 58

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.95 min, ES+ =625.21.

Example 59

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.96 min, ES+ =601.03.

Example 60

4-{4-[2-(2,3,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,3,6-trifluorophenol. LC-MS: R_t =0.92 min, ES+ =591.01.

Example 61

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.96 min, ES+ =659.17.

Example 62

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T1** and 2,4,6-trifluorophenol. LC-MS: R_t =0.94 min, ES+ =625.19.

Example 63

4-{4-[2-(2,6-Difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,6-difluoro-3-methylphenol. LC-MS: R_t =0.94 min, ES+ =587.14.

Example 64

4-{4-[2-(4-Chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to the general procedures F and B, starting from compound **T3** and 4-chloro-2-methoxyphenol. LC-MS: R_t =0.93 min, ES+ =601.18.

Example 65

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T11** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.95 min, ES+ =629.05.

Example 66

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.95 min, ES+ =630.94

Example 67

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T7** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.95 min, ES+ =656.12.

Example 68

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T12** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.93 min, ES+ =611.04.

Example 69

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T8** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.95 min, ES+ =587.03.

Example 70

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.94 min, ES+ =583.26.

Example 71

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.97 min, ES+ =633.11.

Example 72

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide formate salt

According to the general procedures F and B, starting from compound **T9** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.94 min, ES+ =573.07.

Example 73

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T13** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.93 min, ES+ =581.09.

Example 74

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 3-chloro-2,6-difluorophenol. LC-MS: R_t =0.93 min, ES+ =567.24.

Example 75

4-{4-[2-(Benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and benzo[1,3]dioxol-5-ol. LC-MS: R_t =0.94 min, ES+ =625.19.

Example 76

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T6** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.97 min, ES+ =653.12.

Example 77

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-difluorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T2** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.93 min, ES+ =593.24.

Example 78

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,4-dimethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T14** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.90 min, ES+ =611.06.

Example 79

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,4,6-trifluorophenol. LC-MS: R_t =0.91 min, ES+ =551.30.

Example 80

4-{4-[2-(2-Bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2-bromo-5-fluorophenol. LC-MS: R_t =0.91 min, ES+ =551.30.

Example 81

4-{4-[2-(2,3,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,3,6-trifluorophenol. LC-MS: R_t =0.91 min, ES+ =551.12.

Example 82

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 3-chloro-2,6-trifluorophenol. LC-MS: R_t =0.94 min, ES+ =607.14.

Example 83

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2,4,6-trifluorophenol. LC-MS: R_t =0.91 min, ES+ =601.15.

Example 84

4-{4-[2-(2-Bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and 2-bromo-5-fluorophenol. LC-MS: R_t =0.95 min, ES+ =669.20.

Example 85

4-{4-[2-(Benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and benzo[1,3]dioxol-5-ol. LC-MS: R_t =0.90 min, ES+ =581.17.

Example 86

4-{4-[2-(4-Chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and 4-chloro-2-methoxyphenol. LC-MS: R_t =0.94 min, ES+ =635.16.

Example 87

4-{4-[2-(4-Chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 4-chloro-2-methoxyphenol l. LC-MS: R_t =0.92 min, ES+ =561.29.

Example 88

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T10** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.94 min, ES+ =599.03.

Example 89

4-{4-[2-(2,5-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,5-dichlorophenol. LC-MS: R_t =0.95 min, ES+ =607.20.

Example 90

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide

According to the general procedures F and B, starting from compound **T5** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.95 min, ES+ =559.18.

Example 91

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)-cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T1** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.98 min, ES+ =673.24.

Example 92

4-{4-[2-(2,6-Difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and 2,6-difluoro-3-methylphenol. LC-MS: R_t =0.95 min, ES+ =621.31.

Example 93

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)-amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.96 min, ES+ =599.30.

Example 94

4-{4-[2-(2,5-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T1** and 2,5-dichlorophenol. LC-MS: R_t =0.96 min, ES+ =641.12.

Example 95

4-{4-[2-(2,5-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,5-dichlorophenol. LC-MS: R_t =0.94 min, ES+ =565.23.

Example 96

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2-chloro-4-trifluoromethylphenol phenol. LC-MS: R_t =0.97 min, ES+ =639.14.

Example 97

4-{4-[2-(2-Bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2-bromo-5-fluorophenol. LC-MS: R_t =0.94 min, ES+ =634.92.

Example 98

4-{4-[2-(2,3-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2,3-dichlorophenol. LC-MS: R_t =0.94 min, ES+ =607.19.

Example 99

4-{4-[2-(2-Chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 2-chloro-5-fluorophenol. LC-MS: R_t =0.93 min, ES+ =591.21.

Example 100

4-{4-[2-(2,5-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2,5-dichlorophenol. LC-MS: R_t =0.94 min, ES+ =617.11.

Example 101

4-{4-[2-(4-Chloro-2-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T3** and 4-chloro-2-methylphenol. LC-MS: R_t =0.95 min, ES+ =587.22.

Example 102

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T6** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.95 min, ES+ =639.22.

Example 103

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T10** and 2,4,6-trifluorophenol. LC-MS: R_t =0.89 min, ES+ =571.24.

Example 104

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T12** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.92 min, ES+ =615.27.

Example 105

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T10** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.93 min, ES+ =579.15.

Example 106

4-{4-[2-(5-Chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 4-chloro-2-methoxyphenol. LC-MS: R_t =0.91 min, ES+ =613.21.

Example 107

4-{4-[2-(2,3,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2,3,6-trifluorophenol. LC-MS: R_t =0.91 min, ES+ =601.09.

Example 108

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T12** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.93 min, ES+ =591.18.

Example 109

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.95 min, ES+ =611.09.

Example 110

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T8** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.93 min, ES+ =589.27.

Example 111

4-{4-[2-(2,6-Difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,6-difluoro-3-methylphenol. LC-MS: R_t =0.92 min, ES+ =547.37.

Example 112

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T10** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.92 min, ES+ =603.24.

Example 113

4-{4-[2-(2,6-Difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2,6-difluoro-3-methylphenol. LC-MS: R_t =0.92 min, ES+ =599.21.

Example 114

4-{4-[2-(2-Fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T1** and 4-chloro-2-methylphenol. LC-MS: R_t =0.96 min, ES+ =619.23.

Example 115

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T11** and 2,4,6-trifluorophenol. LC-MS: R_t =0.91 min, ES+ =601.19.

Example 116

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T11** and 2,6-difluoro-3-chlorophenol. LC-MS: R_t =0.92 min, ES+ =617.19.

Example 117

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-difluorobenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T2** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.94 min, ES+ =587.14.

Example 118

4-{4-[2-(2,4,5-Trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T1** and 2,4,5-trichlorophenol. LC-MS: R_t =0.98 min, ES+ =675.22.

Example 119

4-{4-[2-(2-Chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropyl-amide formate salt

According to the general procedures F and B, starting from compound **T1** and 2-chloro-5-fluorophenol. LC-MS: R_t =0.94 min, ES+ =623.29.

Example 120

4-{4-[2-(2,3-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,3-dichlorophenol. LC-MS: R_t =0.93 min, ES+ =565.28.

Example 121

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide formate salt

According to the general procedures F and B, starting from compound **T9** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.93 min, ES+ =579.15.

Example 122

4-{4-[2-(2,4,5-Trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and 2,4,5-trichlorophenol. LC-MS: R_t =0.96 min, ES+ =599.32.

Example 123

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 3-chloro-2,3-difluorophenol. LC-MS: R_t =0.93 min, ES+ =619.11.

Example 124

4-{4-[2-(Benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T5** and benzo[1,3]dioxol-5-ol. LC-MS: R_t =0.89 min, ES+ =541.32.

Example 125

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)-amide formate salt

According to the general procedures F and B, starting from compound **T12** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.94 min, ES+ =631.27.

Example 126

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T12** and 2,4,6-trifluorophenol. LC-MS: R_t =0.89 min, ES+ =583.24.

Example 127

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide formate salt

According to the general procedures F and B, starting from compound **T9** and 2,4,6-trifluorophenol. LC-MS: R_t =0.90 min, ES+ =545.24.

Example 128

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxy-benzyl)amide formate salt

According to the general procedures F and B, starting from compound **T10** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.94 min, ES+ =619.26.

Example 129

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T11** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.94 min, ES+ =633.25.

Example 130

4-{4-[2-(4-Chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T13** and 4-chloro-2-methoxyphenol. LC-MS: R_t =0.89 min, ES+ =563.26

Example 131

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.96 min, ES+ =651.16.

Example 132

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T13** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.93 min, ES+ =601.26.

Example 133

4-{4-[2-(2,3,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide formate salt

According to the general procedures F and B, starting from compound **T9** and 2,3,6-trifluorophenol. LC-MS: R_t =0.90 min, ES+ =545.04.

Example 134

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T10** and 2,6-difluoro-3-chlorophenol. LC-MS: R_t =0.91 min, ES+ =587.21.

Example 135

4-{4-[2-(2-Bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T12** (50 mg) and 2-bromo-5-fluorophenol. LC-MS: R_t =0.90 min, ES+ =613.03.

Example 136

4-{4-[2-(2,5-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T12** and 2,5-dichlorophenol. LC-MS: R_t =0.92 min, ES+ =597.23.

Example 137

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T13** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.92 min, ES+ =561.14.

Example 138

4-{4-[2-(4-Chloro-2-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide formate salt

According to the general procedures F and B, starting from compound **T4** and 4-chloro-2-methylphenol. LC-MS: R_t =0.94 min, ES+ =597.20.

Example 139

4-{4-[2-(4-Chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T11** and 4-chloro-2-methoxyphenol. LC-MS: R_t =0.91 min, ES+ =611.23.

Example 140

4-{4-[2-(2-Bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T4** and 2-bromo-4-fluorophenol. LC-MS: R_t =0.92 min; ES+ =645.08.

Example 141

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide

According to the general procedures F and B, starting from compound **T13** and 2,6-difluoro-3-chlorophenol. LC-MS: R_t =0.90 min, ES+ =569.23.

Example 142

4-{4-[2-(2-Chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T11** and 2-chloro-4-trifluoromethylphenol. LC-MS: R_t =0.95 min, ES+ =649.22.

Example 143

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2-chloro-4,5-dimethylphenol. LC-MS: R_t =0.94 min, ES+ =565.28.

Example 144

4-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,6-dichloro-4-methylphenol. LC-MS: R_t =0.95 min, ES+ =587.22.

Example 145

4-{4-[2-(2,4,5-Trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,4,5-trichlorophenol. LC-MS: R_t =0.95 min, ES+ =607.19.

Example 146

4-{4-[2-(2-Chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2-chloro-5-fluorophenol. LC-MS: R_t =0.91 min, ES+ =555.26.

Example 147

4-{4-[2-(2-Chloro-3,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2-chloro-3,6-difluorophenol. LC-MS: R_t =0.91 min, ES+ =573.21.

Example 148

4-{4-[2-(2-Chloro-6-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2-chloro-6-methylphenol. LC-MS: R_t =0.92 min, ES+ =551.30.

Example 149

4-{4-[2-(2,3-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,3-dichlorophenol. LC-MS: R_t =0.92 min, ES+ =571.21.

Example 150

4-{4-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,6-dichloro-4-fluorophenol. LC-MS: R_t =0.93 min, ES+ =589.20.

Example 151

4-{4-[2-(3-Chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 3-chloro-2,6-difluorophenol. LC-MS: R_t =0.91 min, ES+ =573.24.

Example 152

4-{4-[2-(2,4,6-Trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,4,6-trifluorophenol. LC-MS: R_t =0.90 min, ES+ =557.28.

Example 153

4-{4-[2-(2,5-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,5-dichlorophenol. LC-MS: R_t =0.93 min, ES+ =573.21.

Example 154

4-{4-[2-(2,6-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide formate salt

According to the general procedures F and B, starting from compound **T15** and 2,6-dichlorophenol. LC-MS: R_t =0.92 min, ES+ =573.20.

The following assay was carried out in order to determine the activity of the compounds of general formula **I** and their salts.

Inhibition of human recombinant renin by the compounds of the invention

The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 µL per well of an enzyme mix and 2.5 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

- human recombinant renin (0.16 ng/mL)
- synthetic human angiotensin(1-14) (0.5 µM)
- hydroxyquinoline sulfate (1 mM)

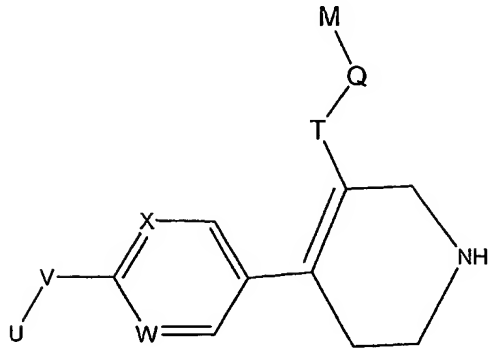
The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 µL of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 µL of Ang I-antibodies in assay buffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After

washing the plates 3 times, the peroxidase substrate ABTS (2.2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at rt. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50}-values of all compounds tested are below 100 nM. However selected compounds exhibit a very good bioavailibility and are metabolically more stable than prior art compounds.

Claims

1. Compounds of the general formula **I**



General formula **I**

wherein

X and W represent independently a nitrogen atom or a CH-group;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O- ; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; $-COO-$; $-(CH_2)_pOCONR^1-$; $-(CH_2)_pN(R^{1'})CONR^1-$;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

R^1 and $R^{1'}$ independently represent hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4 or 5;
t is the integer 1, 2, 3 or 4;
u is the integer 1, 2 or 3;
v is the integer 2, 3 or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Compounds of general formula **I** wherein X, W, V, and U are as defined in general formula **I** and

T represents -$CONR^1$-;
Q represents methylene;
M represents hydrogen; aryl; heteroaryl;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

3. Compounds of general formula **I** wherein X, W, T, Q, and M are as defined in general formula **I** and

V represents

$-CH_2CH_2O-$; $-CH_2CH_2CH_2O-$; $-OCH_2CH_2O-$,

and U is as defined in general formula **I**,

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

4. Compounds of general formula **I** wherein V, U, T, Q, and M are as defined in general formula **I** above, wherein

X and Wrepresents CH;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

5. Compounds of general formula **I** wherein X, W, V, Q, T, and M are as defined in general formula **I** above, wherein

U represents a mono-, di-, or trisubstituted phenyl and the substituents are independently halogen, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

6. The compounds according to any one of claims 1 - 5 selected from the group consisting of

4-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid 2-phenethylmethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid (2-chlorobenzyl)methylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridi-ne-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide,

4-{4-[3-(2-chlorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid 2-phenethylmethylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)methylamide,

4-{4-[3-(2,5-difluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluorobenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*m*-tolyloxyethyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-fluorophenyl)ethyl]amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*o*-tolylethyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide,

4-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethylbenzyl)amide,

4-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide,

4-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropylphenethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-methylbenzyl)amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropylphenethylamide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-*o*-tolylethyl)amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,4-dimethoxybenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-6-fluorobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-fluoro-2-methylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methylbenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-difluorobenzyl)amide,

4-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-difluorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,4-dimethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)-cyclopropylamide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,3-Dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(4-chloro-2-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-trifluoromethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(5-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (3-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,6-difluoro-3-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3,5-difluorobenzyl)amide,

4-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chloro-3-trifluoromethylbenzyl)cyclopropylamide,

4-{4-[2-(2,3-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(benzo[1,3]dioxol-5-yloxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(2,3,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)ethylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-fluoro-5-methoxybenzyl)amide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid cyclopropyl-(3,5-dimethoxybenzyl)amide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(4-chloro-2-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2,3-dimethylbenzyl)amide,

4-{4-[2-(4-chloro-2-methoxyphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-bromobenzyl)cyclopropylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(3-methoxybenzyl)amide,

4-{4-[2-(2-chloro-4-trifluoromethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (6-chlorobenzo[1,3]dioxol-5-ylmethyl)-cyclopropylamide,

4-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-3,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2-chloro-6-methylphenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,3-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,6-dichloro-4-fluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(3-chloro-2,6-difluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,4,6-trifluorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide,

4-{4-[2-(2,5-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide, and

4-{4-[2-(2,6-dichlorophenoxy)ethoxy]phenyl}-1,2,5,6-tetrahydropyridine-3-carboxylic acid (2-chlorobenzyl)cyclopropylamide.

7. Pharmaceutical compositions containing a compound of any one of claims 1 - 6 and usual carrier materials and adjuvants for the treatment or prophylaxis of

disorders which are associated with a dysregulation of the renin-angiotensin system (RAS), comprising cardiovascular and renal diseases, hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases presently known to be related to the RAS.

8. A method for the treatment or prophylaxis of diseases which are related to the RAS including hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases which are related to the RAS, which method comprises administrating a compound according to any one of claims 1 to 6 to a human being or animal.

9. The use of compounds according to any one of claims 1 to 6 for the treatment or prophylaxis of diseases which are associated with the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases presently known to be related to the RAS.

10. The use of one or more compounds of any one of claims 1 to 6 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics,

beta-adrenergic antagonists, alpha-adrenergic antagonists, for the treatment of disorders given in any one of claims 7 to 9.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04445

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/78 C07D405/12 A61K31/451 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 64873 A (HOFFMANN LA ROCHE) 2 November 2000 (2000-11-02) page 1 -page 2, line 2	1-10
A	GULLER R ET AL: "Piperidine-renin inhibitors compounds with improved physicochemical properties" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 10, 17 May 1999 (1999-05-17), pages 1403-1408, XP004164901 ISSN: 0960-894X tables 1,2	1-10
A	WO 97 09311 A (HOFFMANN LA ROCHE) 13 March 1997 (1997-03-13) page 1, line 1 -page 6, line 5 page 64, line 12 -page 64, line 29	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2003	04/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Usuelli, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/04445

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/04445

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